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# METHOD FOR PREPARATION OF 2-AMINOALKYL-3,4-DIHYDRO-4-OXO-7H-PYRROLO[2.3-d]PYRIMIDINES

[Verfahren zur Herstellung von 2-Aminoalkyl-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidinen]

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| TITLE | (54): | METHOD FOR PREPARATION OF 2-AMINOALKYL-3,4-DIHYDRO-4-OXO-7H-PYRROLO[2.3-d]PYRIMIDINES |
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Claim

A method for preparation of 2-aminoalkyl-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidines of the general formula I,

in which

$R^1$ = alkyl,

$R^2$ and $R^3$ = H, alkyl, heteroalkylene, aryl

characterized by the fact that 5-alkylthio-2-amino-3,4-dicarbamoyl-1H-pyrroles of the general formula IV, in which

$R^1$ = alkyl

are reacted with α-haloacyl halides in an organic solvent to form 5-alkylthio-3,4-dicarbamoyl-2-(α-halogenacylamino)-1H-pyrroles of the general formula II, in which

$R^1$ = alkyl,

which then react in a reaction with amines in an organic solvent to form 5-alkylthio-2-(α-aminoacylamino)-3,4-dicarbamoyl-1H-pyrroles of the general formula III, in which

$R^1$, $R^2$ and $R^3$ have the meanings given above, which in a last step cyclize under basic conditions to form the end products of general formula I.

1 page of formulas is attached

Field of the invention

The invention concerns a method for synthesis of 2-aminoalkyl-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidines of the general formula,

in which

$R^1$ = alkyl,

$R^2$ and $R^3$ = H, alkyl, heteroalkylene, aryl.

The compounds are potential drugs and at the same time are intermediate products in the pharmaceutical industry.

Description of known technical solutions

Compounds of general formula I have not been described neither in the patent literature nor in the special literature. Thus, 2-aminoalkyl-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidine derivatives with the above substitution pattern are prepared for the first time, while up to now primarily 4-aminopyrrolo[2.3-d]pyrimidines (DE 3036390; DE 3111155; DE 2818676, EP 5205; US 3988338; Chem. Ber. 109 (9):2983-95, 1976; J. Amer. Chem. Soc. 87 (9): 1995-2003, 1965) and 2-amino-5-aminomethylpyrrolo[2.3-d]pyrimidines (EP 79447; EP 119591) have been prepared and tested.

Goal of the invention

The goal of the invention is to develop a simple and rapid method for producing hitherto unavailable 2-aminoalkyl-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidines of general formula I with readily available starting materials in order to broaden the available range of potential drugs or intermediate products of interest in this way.

Nature of the invention

The task of the invention is [to specify] a method for synthesis of 2-aminoalkyl-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidines of the general formula I,

in which

$R^1$ = alkyl,

$R^2$ and $R^3$ = H, alkyl, heteroalkylene, aryl.

In accordance with the invention, the task is solved by the fact that 5-alkylthio-2-amino-3,4-dicarbamoyl-1H-pyrroles of general formula IV,

in which $R^1$ = alkyl,

are reacted with α-haloacyl halides in an organic solvent. The resulting 5-alkylthio-2-(α-halogenacylamino)-3,4-dicarbamoyl-1H-pyrroles of the general formula II,

in which

$R^1$ = alkyl,

are reacted with amines in an organic solvent. The substituted 5-alkylthio-2-(α-aminoacylamino)-3,4-dicarbamoyl-1H-pyrroles of general formula III,

in which $R^1$ = alkyl,

$R^2$ and $R^3$ = H, alkyl, heteroalkylene, aryl,

that are obtained in this way are cyclized under basic conditions to form the end products of general formula I. The further processing of the intermediate and end products takes place in a substantially known way.

Embodiment examples

The invention is explained below by means of three embodiment examples.

Example 1

Preparation of 2-(chloroacetylamino)-3,4-dicarbamoyl-5-methylthio-1H-pyrrole

$C_9H_{11}ClN_4O_3S$ (290.70)

0.01 mol 2-amino-3,4-dicarbamoyl-5-methylthio-1H-pyrrole is dissolved in 25 mL dimethylformamide. 0.01 mol chloroacetyl chloride is added by drops to this solution and the mixture is stirred for 1 h at room temperature. It is then poured into water and the precipitate that forms is vacuum-filtered out.

The product is recrystallized from methanol.

Melting point: 243-245°C

Yield: 79%

The following was prepared analogously:

2-(Chloroacetylamino)-3,4-dicarbamoyl-5-ethylthio-1H-pyrrole, $C_{10}H_{13}ClN_4O_3S$ (304.75)

Melting point: 197-199°C, yield: 84%.

Example 2

Preparation of 3,4-dicarbamoyl-5-methylthio-2-(morpholinoacetylamino)-1H-pyrrole

$C_{13}H_{19}N_5O_4S$ (341.39)

0.02 mol morpholine is added to 0.01 mol 2-(chloroacetylamino)-3,4-dicarbamoyl-5-methylthio-1H-pyrrole in 20 mL dimethylformamide. After cooling, the reaction mixture is poured into water and the precipitate is vacuum-filtered out.

The product is recrystallized from ethanol.

Melting point: 272-275°C.

Yield: 74%.

The compounds listed in Table 1 are prepared analogously.

TABLE 1. Compounds according to formula III

| ① Nr. | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| 1 | $CH_3$ | H | $C_6H_5$ |
| 2 | $CH_3$ | H | o-$CH_3C_6H_4$ |
| 3 | $CH_3$ | H | o-$CH_3OC_6H_4$ |
| 4 | $CH_3$ | H | o,m-$(CH_3)_2$-$C_6H_3$ |
| 5 | $CH_3$ | H | m-$CH_3C_6H_4$ |
| 6 | $CH_3$ | H | m-$ClC_6H_4$ |
| 7 | $CH_3$ | H | o-$ClC_6H_4$ |

| ① Nr. | ② Summenformel | ③ Molmasse | ④ Ausbeute (%) | ⑤ Schmelzpunkt (°C) |
|---|---|---|---|---|
| 1 | $C_{15}H_{17}N_5O_3S$ | 347,39 | 75 | 228–30 |
| 2 | $C_{16}H_{19}N_5O_3S$ | 361,42 | 84 | 233–35 |
| 3 | $C_{16}H_{19}N_5O_4S$ | 377,42 | 72 | 157–59 |
| 4 | $C_{17}H_{21}N_5O_3S$ | 375,45 | 87 | 210–13 |
| 5 | $C_{16}H_{19}N_5O_3S$ | 361,42 | 82 | 205–07 |
| 6 | $C_{16}H_{16}ClN_5O_3S$ | 381,84 | 75 | 182–84 |
| 7 | $C_{15}H_{16}ClN_5O_3S$ | 381,84 | 65 | 231–32 |

Key: 1 No.
2 Formula
3 Molecular weight
4 Yield (%)
5 Melting point (°C)

In addition, the following derivatives were prepared analogously:

3,4-Dicarbamoyl-5-ethylthio-2-(morpholinoacetylamino)-1H-pyrrole, $C_{14}H_{21}N_5O_4S$ (355.41)

Melting point: 239-40°C

Yield: 79%

3,4-Dicarbamoyl-5-ethylthio-2-(1,2,3,4-tetrahydroisoquinolinoacetylamino)-1H-pyrrole, $C_{19}H_{22}N_5O_3S$ (401.50)

Melting point: 235-36°C

Yield: 82%

3,4-Dicarbamoyl-5-methylthio-2-(1,2,3,4-tetrahydroisoquinolinoacetylamino)-1H-pyrrole, $C_{18}H_{21}N_5O_3S$ (387.46)

Melting point: 278-80°C

Yield: 87%

Example 3

Preparation of 5-carbamoyl-6-methylthio-2-morpholinomethyl-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidine

$C_{13}H_{17}N_5O_4S$ (323.37)

0.01 mol 3,4-dicarbamoyl-5-methylthio-2-(morpholinoacetylamino)-1H-pyrrole is dissolved in 25 mL sodium hydroxide (4 mol/L) and boiled for 2 min. After cooling the solution it is neutralized with HCl (2 mol/L) and the precipitate is vacuum-filtered out. Melting point 355-57°C.

Yield: 70%

The compounds listed in Table 2 are prepared analogously.

TABLE 2. Compounds in accordance with formula I

| ① Nr. | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| 1 | $CH_3$ | H | $C_6H_5$ |
| 2 | $CH_3$ | H | o-$CH_3C_6H_4$ |
| 3 | $CH_3$ | H | o-$CH_3OC_6H_4$ |
| 4 | $CH_3$ | H | o,m-$(CH_3)_2$-$C_6H_3$ |
| 5 | $CH_3$ | H | m-$CH_3C_6H_4$ |
| 6 | $CH_3$ | H | m-$ClC_6H_4$ |
| 7 | $CH_3$ | H | o-$ClC_6H_4$ |

| ① Nr. | ② Summenformel | ③ Molmasse | ④ Ausbeute (%) | ⑤ Schmelzpunkt (°C) |
|---|---|---|---|---|
| 1 | $C_{15}H_{15}N_5O_2S$ | 329,38 | 77 | 253–55 |
| 2 | $C_{16}H_{17}N_5O_2S$ | 343,41 | 81 | 210–12 |
| 3 | $C_{16}H_{17}N_5O_3S$ | 359,41 | 79 | 201–02 |
| 4 | $C_{17}H_{19}N_5O_2S$ | 357,44 | 80 | 190–92 |
| 5 | $C_{16}H_{17}N_5O_2S$ | 343,41 | 75 | 178–79 |
| 6 | $C_{15}H_{14}ClN_5O_2S$ | 363,82 | 72 | 240–41 |
| 7 | $C_{15}H_{14}ClN_5O_2S$ | 363,82 | 60 | 271–72 |

Key: 1 No.

2 Formula

3 Molecular weight

4 Yield (%)

5 Melting point (°C)

In addition, the following derivatives were prepared analogously:

5-Carbamoyl-6-ethylthio-2-(morpholinomethyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidine

$C_{14}H_{19}N_5O_3S$ (337.39)

Melting point: 210-12°C

Yield: 75%

5-Carbamoyl-6-ethylthio-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidine

$C_{19}H_{21}N_5O_2S$ (383.46)

Melting point: 220-21°C

Yield: 72%

5-Carbamoyl-6-methylthio-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-3,4-dihydro-4-oxo-7H-pyrrolo[2.3-d]pyrimidine

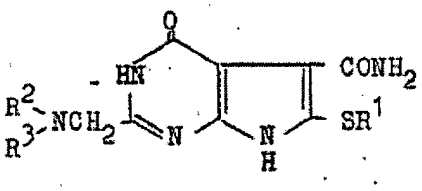
$C_{18}H_{19}N_5O_2S$ (369.44)

Melting point: 238-40°C

Yield: 73%

Formulas

① Formel I



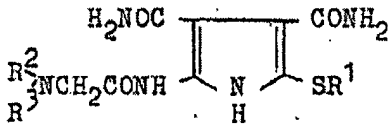
$R^1$ = alkyl

$R^2$,$R^3$ = H, alkyl, heteroalkylen, aryl ②

①Formel II

$R^1$ = alkyl

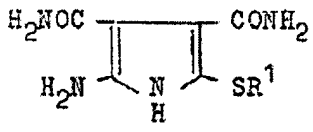
Formel III



$R^1$ = alkyl

$R^2$,$R^3$ = H, alkyl, heteroalkylen, aryl ②

① Formel IV



$R^1$ = alkyl

Key: 1 Formula ...
2 H, alkyl, heteroalkylene, aryl